Remarks

Applicant respectfully requests reconsideration. Claims 104-110 and 112-114 are pending and currently under examination in this application with claim 104 being an independent claim. By this Response no claims are canceled, amended, or added. No new matter has been added.

Claim Objections

Applicant acknowledges that the Examiner indicated Claim 114 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant believes the arguments presented below obviate the objection to claim 114.

Claim Rejections Under 35 U.S.C. §103

Claims 104-110 and 112-113 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over McKay et al., U.S. Patent No. 5,877,309 (hereinafter, "McKay") taken together with Schlom et al., U.S. Patent No. 6,045,802 (hereinafter, "Schlom").

Claim 104 of the instant application is directed to a method for treating a subject having a tumor, the method comprising administering to a vertebrate subject having a tumor a tumor-specific antigen and an oligonucleotide 10-50 nucleotides long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, and GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide, in order to treat the subject.

McKay teaches compositions and methods for treating various hyperproliferative disorders or diseases, including cancer, by modulation of JNK expression with specifically hybridizable antisense oligonucleotides. As pointed out by the examiner, one such antisense oligonucleotide, SEQ ID NO:24, happens to be between 10-50 nucleotides long, comprise the sequence GAGGG, and not comprise a CG dinucleotide.

Activation of JNK would be expected to increase cell proliferation, tumor formation, and tumor growth, whereas inhibition of JNK would be expected to inhibit cell proliferation, tumor

formation, and tumor growth. JNK proteins act to transduce extracellular signals into the cell, which often results in the activation of transcription factors. For example, JNK activates the AP-1 family of transcription factor complexes, which can activate cell proliferation. JNK is aberrantly expressed in some neoplasms and tumors, and at least one leukemia oncogene has been reported to enhance JNK function. In the immune system, JNK is often activated as part of mounting an immune response. It is expressed in cells of the immune system, such as T cells, macrophages, and dendritic cells. JNK transduces signals that lead to the production of cytokines, induction of stress responses, and proliferation of cells of the immune system. The activity of JNK, along with other key MAP kinases, must be shut off in order to terminate T-cell activation and avoid runaway immune activation.

Although McKay defines "modulation" of JNK expression as either "an increase (stimulation) or a decrease (inhibition) in the expression of the protein" (column 4, lines 56-58), McKay as a whole teaches only methods for *inhibition* of JNK expression. For example, McKay specifically teaches

> Modulation of the expression of one or more JNK proteins is desirable in order to interfere with hyperproliferation of cells and with the transcription of genes stimulated by AP-1 and other JNK protein phosphorylation substrates. Modulation of one or more other JNK proteins is also desirable in order to interfere with hyperproliferation of cells resulting from abnormalities in specific signal transduction pathways. To date, there are no known therapeutic agents which effectively inhibit gene expression of one or more JNK proteins. Consequently, there remains a long-felt need for improved compositions and methods for modulating the expression of specific JNK proteins.

McKay, Column 2, line 62 ff; emphasis added. Given the role of JNK in inducing cell proliferation and gene transcription (above), it is clear from this passage that "modulating the expression of specific JNK proteins" in McKay refers to interfering with hyperproliferation of cells by inhibiting gene expression of one or more JNK proteins. Indeed, in McKay at column 4, lines 58-60, it is stated "[i]n the context of the present invention, inhibition is the preferred form of modulation of gene expressio[n]". In addition, McKay gives as examples only those directed specifically to inhibition of JNK expression. For instance, Example 2 of McKay describes oligonucleotide-mediated inhibition of JNK mRNA. Example 3 of McKay lists JNK-specific antisense oligonucleotide sequences, the percent inhibition of JNK for each in the experiment, a

time course of JNK inhibition, and dose-dependent inhibition of JNK1 by antisense oligonucleotides. Likewise, Examples 4 and 5 of McKay are directed to inhibition of JNK2 and JNK3, respectively, through the employment of the methods of the invention. In short, McKay offers no examples directed to activation of JNK. Therefore, the teachings of McKay taken as a whole are directed to inhibition of aberrant cellular proliferation through antisense oligonucleotide-mediated inhibition of JNK expression.

In contrast, Schlom teaches use of viral vectors comprising the coding sequence for a tumor antigen, and optionally a gene encoding one or more immunostimulatory molecules, to treat a cancer. The vector encoding an antigen directs expression of the antigen so as to elicit and/or upregulate an immune response in a mammal to T-dependent antigens, i.e., to induce or increase an immune response directed against the tumor antigen-expressing tumor. Schlom, column 6-7. The examiner points out on page 4 that Schlom teaches that there are several antigens known in the prior art for use in cancer therapy. For the record, Applicant notes it is clear from Schlom that a gene encoding one or more immunostimulatory molecules does not include an oligonucleotide 10-50 nucleotides long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, and GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide.

The examiner points out on page 3 that McKay teaches that it would be more effective to treat a patient with a JNK antisense oligonucleotide in conjunction with other traditional therapeutic methods in order to increase the efficacy of a treatment regimen (emphasis added). On page 4 the examiner goes on to state that one of ordinary skill in the art would have been motivated to use a tumor specific antigen in the method taught by [Schlom] because a tumor specific antigen would improve the effectiveness of the method taught by McKay for treating a tumor in a subject. Applicant respectfully disagrees.

Applicant respectfully submits the Examiner has not made a *prima facie* case for an obviousness rejection based on a combination of the McKay and Schlom references. In order to make a *prima facie* case for an obviousness rejection based on combining two or more references, the examiner must show some specific teaching, suggestion, or motivation provided by the references to make the combination. Here it is evident that McKay teaches inhibiting cellular proliferation, while Schlom teaches a method for inducing antigen-specific clonal

expansion of T cells, i.e., cellular proliferation, in the immune system. As noted above, in many cell types of the immune system, including T cells in particular, upregulation of JNK expression plays an pivotal role in inducing an immune response. There is no teaching, suggestion, or motivation provided in McKay and/or Schlom to combine a method for downregulating JNK (as in McKay) with a method in which JNK may be upregulated (as in Schlom) as these methods appear to be mutually contradictory. Accordingly, Applicant submits that there is no teaching, suggestion, or motivation to combine the teachings of McKay and Schlom as proposed by the examiner. Applicant therefore respectfully submits the examiner has not made a *prima facie* case for making the obviousness rejection and accordingly requests the examiner to reconsider and withdraw the rejection of claims 104-110 and 112-113 under 35 U.S.C. § 103(a).

Further, even if one were to attempt to combine the teachings of McKay with the teachings of Schlom, there would be no reasonable expectation of success in arriving at the instantly claimed invention. Administration of an antisense oligonucleotide specific for JNK (as in McKay) to cells which are to be activated to produce an immune response against a tumor-specific antigen (as in Schlom) would be expected to have the effect of inhibiting the normal JNK activities involved in and necessary for mounting an effective immune response. The combination proposed by the examiner would therefore be expected to inhibit an immune response and perhaps even result in tolerizing the subject to any co-administered tumor-specific antigen. Such outcomes obviously would not improve the effectiveness of the method taught by McKay for treating a tumor in a subject. Rather, the combination proposed by the examiner would be expected to exacerbate a tumor in a subject and therefore lead to a result entirely opposite to what is desired. Accordingly, Applicant submits that a person skilled in the art, at the time the invention was made, would have no reasonable expectation of success in combining the methods of McKay and Schlom. Applicant therefore respectfully requests the examiner to reconsider and withdraw the rejection of claims 104-110 and 112-113 under 35 U.S.C. § 103(a).

Summary

No claims are canceled, amended, or added by this Response. Arguments are set forth to overcome all claim rejections and objection to claim 114. A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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